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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,375	07/29/2003	Michel Schneider	BR029-US-02	8951

7590  
Bracco Research USA  
305 College Road East  
Princeton, NJ 08540

EXAMINER
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EBRAHIM, NABILA G

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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10/24/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/630,375	<b>Applicant(s)</b> SCHNEIDER ET AL.	
	<b>Examiner</b> Nabila G. Ebrahim	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) 1-15 and 33-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 16-32 and 47-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Receipt of Applicant's arguments dated 02/26/2008 is acknowledged.

#### ***Status of Claims***

Claims 1-52 are pending in the application.

Claims 16-32 and 47-52 are under current examination.

Claims 1-15 and 33-46 were withdrawn from consideration due to election/restriction requirement.

***Status of Office Action:*** Final.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

1. Claim 16-32 and 47-52 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tournier et al. US 6042809 (Tournier).

Tournier teaches compositions for MR imaging, the composition comprises one or more film-forming surfactant such as phosphatidylcholine (DSPC, see example 2), and a gas in a physiological saline (col. 5, lines 51+ bridging to col. 1, lines 1+). Regarding the gas pressure Tournier discloses that the values in Table 1 correspond to the pressure (over atmospheric) at which about half of the bubbles originally present are destroyed, the disclosure teaches indirectly that the pressure of the microvesicles should be less than the atmospheric pressure. Further table 2 shows that the gases used in the composition may be xenon or perfluorobutane C<sub>4</sub>F<sub>10</sub> or mixtures (see example 2, tables 2, 4, 5 and claim 4). The dry formulation comprises lyophilized film forming surfactants and, optionally, hydrating agents like polyethylene glycol (col. 7, lines 56+ bridging to col. 8, lines 1+). The container recited in the claims is a logical means wherein the ingredients were mixed; however, Tournier discloses a kit comprising the

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components required to in situ produce the foregoing administrable compositions (col. 3, lines 47+). The composition is injectable as required by claim 32 (example 1). Further Tournier teaches that the composition comprises viscosity enhancers or stabilizers selected from linear and cross-linked poly- and oligo-saccharides, sugars, hydrophilic polymers and iodinated compounds (claim 6). Regarding the reconstitution property of the composition, it is considered an inherent property that the same composition of the prior art would be capable of performing.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-32 and 47-52 remain rejected under 35 U.S.C. 103(a) as being obvious over Tournier et al. US 6042809 (Tournier) in view of Hugh D. Van Liew, Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, *J Appl Physiol* 82:2045-2053, 1997 (hereinafter Hugh).

Tournier teaches the same invention as shown hereinabove, the reference does not teach literally that the pressure of the gas should be less than atmospheric pressure.

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Hugh teaches Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, the reference discloses that The crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that the pressure inside the gas microvesicles disclosed by Tournier should be less than the atmospheric pressure to counter the tendency for outward diffusion of the gases as disclosed by Hugh. The skilled artisan would have success expectations to have a composition for contrast agent in an aqueous suspension containing gas-filled microvesicles useful in imaging.

### ***Double Patenting***

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 16, 21-24, 28-32 and 47-52 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6485705, 6403057, 6896875, 6592846, 6613306, 6187288, 6042809, 5911972, 6183725,

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6136293 in view of Hugh D. Van Liew, Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, *J Appl Physiol* 82:2045-2053, 1997. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all drawn to compositions comprising the same components, such as, gas microbubble compositions or dry precursors thereof having a phospholipid as a film forming surfactant and a hydrophilic stabilizer that comprises PEG, and mainly only differ in the wording of the claims and genus species situations. For example, Patent '288 recites a composition comprising phosphatidylcholine, hydrophilic polymer such as PEG, and a physiologically acceptable fluorine containing gas. These claims differ is encompassed by instant claim 1 while claim 15 of '288 which recites the fluorinated gas encompass the perfluorobutane recited in the instant claims.

None of the patents claims recite the gas reduced pressure.

Hugh teaches Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, the reference discloses that The crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that the pressure inside the gas microvesicles should be less than the atmospheric pressure to counter the tendency for outward diffusion of the gases as disclosed by Hugh. The skilled artisan would have success expectations to have a composition for contrast agent in an aqueous suspension containing gas-filled microvesicles useful in imaging

6. Claims 16, 21-24, 28-32 and 47-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/544123, 10/584327, 10/584382, 10/725777, 10/831165, 11/058169, 11/202008, 11/660188, 11/851769 in view of Hugh D. Van Liew, Stabilized bubbles

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in the body: pressure-radius relationships and the limits to stabilization, *J Appl Physiol* 82:2045-2053, 1997.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all drawn to compositions comprising the same components, such as, gas microbubble compositions or dry precursors thereof having a phospholipid as a film forming surfactant and a hydrophilic stabilizer such as PEG, and mainly only differ in the wording of the claims and genus species situations.

None of the patents claims recite in the claims the gas reduced pressure.

Hugh teaches Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, the reference discloses that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that the pressure inside the gas microvesicles should be less than the atmospheric pressure to counter the tendency for outward diffusion of the gases as disclosed by Hugh. The skilled artisan would have success expectations to have a composition for contrast agent in an aqueous suspension containing gas-filled microvesicles useful in imaging

This is a provisional obviousness-type double patenting rejection.

### ***Response to Arguments***

7. Applicant's arguments filed 2/26/2008 have been fully considered but they are not persuasive. Applicant argues that:

### ***Rejection under 35 U.S.C. § 102***

- The '809 patent neither teaches nor suggests the use of gas of lower than atmospheric pressure in preparing microvesicles.

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To respond: this was not found persuasive because applicant argues a step in a method. However, instant claims recite a composition which when defined by a process, determination of patentability is based on the product itself. Note that Tournier recognized the problem of instability of the vesicles due to pressure variations, and since the art knew that a negative pressure inside the bubble to counter the tendency of outward diffusion of the gases inside was the solution of the problem (evidenced by Hugh article), it is expected that the stability achieved by Tournier should be having lower pressure than the atmospheric pressure.

- The  $P_c$  value (i.e. the value of pressure chosen to define the resistance of bubbles to external pressure) has no relation at all to the pressure of the gas inside the bubbles or to the pressure of the gas prior to reconstitution.

To respond: This was not found persuasive because teaches that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (see page 2045, right column).

***Rejection under 35 U.S.C. § 103***

- Applicants note that the subject matter of the '809 patent and the instant claims were at the time of invention subject to an obligation of assignment to the same entity; thus, the '809 patent is not proper art for use in an obviousness rejection.

To respond: as demonstrated in the office action dated 12/12/2007, this rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently



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owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Since Applicant had not shown any of the evidence required, the rejection under 35 U.S.C. §103 is maintained.

### ***Double Patenting***

▪ Applicants states that Like the '809 patent and the Van Liew article, the cited patents and applications fail to teach or suggest contacting dried material with a gas at reduced pressure as required by the instant claims. Thus, the cited combinations cannot render Applicants claims obvious. Thus, Applicants request that the double patenting rejections be withdrawn.

To respond: as discussed supra, even if it did not teach literally that the pressure of the gas should be less than atmospheric pressure, Hugh is relied upon for teaching that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

Thus the rejection is maintained.

### ***Conclusion***

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/  
Examiner, Art Unit 1618

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit  
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